REMARKS

Election/Restriction

Applicants acknowledge that the restriction requirement has been made final. Claims 1, 3-23, and 35-36 have been withdrawn from consideration, and will be cancelled upon indication of allowable subject matter.

Claim Rejection

Claims 2, 24-34, and 37-42 are pending in this application, and stand rejected under 35 U.S.C. 103(a) as being unpatentable over Swaan et al. (Bioconjugate Chem. 1997, 520-525) in view of Balschmidt et al. (U.S. Pat. No. 5053389), Fukuda (EP 068052 A2), Kidron et al. (U.S. Pat. No. 4579730), and Yoo (U.S. Pat. No. 6251428). Applicants respectfully traverse this rejection.

To establish prima facie obviousness of a claimed invention under 35 U.S.C. 103(a), three criteria must be met: "First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must a reasonable expectation of success. Finally, the prior art [references] must teach or suggest all the claim limitations." (MPEP 2142).

The claimed invention is directed to a pharmaceutically active substance conjugated with a bile acid via the carboxylic acid group of the bile acid and methods of making and using such conjugates with markedly improved uptake of the active substance into the blood stream. In particular, an insulin peptide is conjugated to a bile acid by an amide bond to the C24 position of the bile acid.

Swaan et al. teach the amide of a bile acid/salt conjugated to various therapeutic small molecular weight peptides through a carboxyl group, so as to enhance oral absorption of the peptides. As the Examiner concedes, Swaan et al. do not teach insulin peptides conjugated with bile acids. Although the Examiner is correct that insulin is "notoriously well recognized in the art as being a small molecular weight therapeutic peptides," insulin is equally well known as having many more than four or six amino acids. In fact, insulin is a protein consisting of two polypeptide chains, one of 21 amino acid residues and the other of 30, joined by two disulfide bridges.

Further, Swaan et al. do not describe attachment of the peptide directly to the C24 position but rather describe attachment via an intervening γ-L-Glu residue. Although this residue is an amino acid, it will not be considered by the skilled person as an amino acid

residue of the attached peptide. This is because that L-Glu residue is not attached to the bile acid via an α-carboxy group as would be expected at the c-terminal position of a peptide chain, but rather, the attachment is via the γ-carboxy group of the L-Glu molecule. Glutamate has two carboxy groups: one is the α-carboxy found in α-amino acids, while the other is a γ-carboxy positioned on a side chain of the glutamate amino acid molecule.

Swaan states that the inclusion of the γ-L-Glu is essential in that it is required to "conserve the specific interaction of these conjugates with the bile acid transporter" because the γ-L-Glu residue provides "the required negative charge around the 24-position" (page 523, col.2, first paragraph, lines 15-19). Swaan then explains that γ-glutamic acid was chosen instead of α-glutamic acid because the γ-Glu contains only one carbon atom between the α-carbon atom and the free carboxylic acid group compared to two carbon atoms in a α-Glu presumably to ensure that the negative charged provided by the free carboxylic acid group remains close to the bile acid portion of the conjugate.

More importantly, the Swaan reference actually teaches away from peptide size of the presently claimed invention. In the Discussion section on page 523 of Swaan, it is stated that small model peptides up to 6 amino acids were coupled to cholic acid. Swaan also teaches that peptides of 4 amino acids in length were attached and these conjugates were absorbed. However, Swaan then reports that conjugates with peptides of 6 amino acids long were not actively taken up, but merely absorbed by passive means – see the statement bridging pages 520-521 and page 524, col. 2, first full paragraph, last sentence with regard to the amino acid peptide conjugate ChEASASA. The next paragraph indicates that no clear conclusions could be drawn. Furthermore, at p. 524, col. 1, lines 17-20, it is stated that peptides with more than 4 Ala residues had very poor solubility and it was necessary to make the peptide more hydrophilic by incorporating Ser residues into the peptide. This is a further example of the clear limitations of the Swaan methods.

Certainly, Swaan provides no motivation whatsoever to consider an attachment that lacks an intervening γ-L-Glu residue and importantly does not motivate the skilled person to use a peptide more than 6 amino acids long. In fact, Swaan teaches that 4 amino acids is really the workable length, and conjugates with peptides of more than 4 amino acids long will not be actively absorbed. Thus, Swaan would not provide one of ordinary skill in the art a reasonable expectation of success to attach a peptide that is significantly longer than 6 amino acids, e.g., 51-amino acid insulin, to a bile acid and achieve the present invention.

Broadly, in each of the other cited references, Balschmidt et al., Fukuda, Kidron et al., and Yoo, only physical mixtures of bile acids (or derivatives thereof) and insulin are described.

In particular, the Examiner considers Fukuda as teaching the amide of a bile acid/salt of formula (II) in a composition with insulin, for enhanced oral absorption, in a pharmaceutical composition, for the treatment of a subject, along with a method of making a pharmaceutical composition thereof. Applicants respectfully disagree with the Examiner's assessment of that document. Fukuda relates to a stabilised insulin solution which is used as a calibration standard and not a pharmaceutical composition for enhanced oral absorption. Moreover, Fukuda only relates to physical mixtures of bile acid and insulin, rather than conjugates of the two, and the same is true for Balschmidt et al.

Similarly, Kildron et al. neither teach nor suggest actually attaching the peptide to the bile acid/salt. In fact, Kildron et al. do not consider this option because that document is concerned with simply mixing the peptide with a bile acid/salt.

Yoo principally relates to the solubilisation of bile acid in solutions with a starch conversion product and the stability of the solutions formed. Applicants note at col. 9, lines 21-27, that additional pharmaceutical compounds may be included in the formulations, including insulin. However, it is specifically stated at col. 9, lines 23-26 that the bile acid in solution may act as an adjuvant, carrier or enhancer for the solubility of the pharmaceutical agents. No mention is made of the use of the bile acid to actually enhance absorption of the pharmaceutical agents in the intestine.

Swaan et al. actually teach away from conjugating peptides longer than four amino acids with bile acid, and none of the cited references provides suggestion or motivation for one of ordinary skill in the art to reconsider those teachings and arrive at the claimed invention. Nor, in light of the teachings of Swaan et al., would one of ordinary skill in the art have any reasonable expectation of success in arriving at the presently claimed invention by combining the prior art references of record.

Applicants further draw the Examiner's attention to another reference made of record in this case in the IDS: Kramer et al., Intestinal absorption of peptides by coupling to bile acids, J. Biol. Chem. 269, p 10624 (1994). In this reference, peptide radicals were attached to the C3 position of a bile acid molecule. Kramer et al. essentially describe, on page 10624, col. 1, in the last sentence of the first full paragraph, that peptide radicals of greater than 4 amino acid residues resulted in a significant drop in absorption. Therefore, Kramer et al. also

teach away from using peptides of greater than 4 amino acids in length. Further, Kramer et al. do not teach any other location for attaching the peptides other than the C3 position.

The fact that an invention proceeds contrary to accepted wisdom in the art is evidence of non-obviousness. (MPEP 2145 X.D.3). *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986). Those skilled in the art would rely on the teachings of Swaan et al. and Kramer et al., which teach away from the claimed invention, and accept their conclusions that conjugating a peptide longer than four amino acids with a bile acid/salt would not achieve the purpose of improving absorption of the peptide. Therefore, the state of the art provides further evidence that the present invention is not obvious.

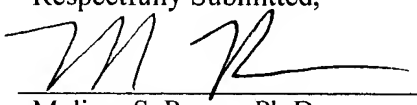
Accordingly, Applicants respectfully submit that a prima facie case of obviousness has not been made.

Conclusion

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited.

Although Applicants believe no fees are due with this submission, the Commissioner is hereby authorized to credit any overpayment or charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 18-1945. Please direct any questions arising from this submission to the undersigned at (617) 951-7000.

Respectfully Submitted,



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